Gas Exchange in the Lung

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Abstract

Gas exchange in the lung depends on tidal breathing, which brings new oxygen to and removes carbon dioxide from alveolar gas. This maintains alveolar partial pressures that promote passive diffusion to add oxygen and remove carbon dioxide from blood in alveolar capillaries. In a lung model without ventilation and perfusion ($\dot{V}_A/\dot{Q}$) mismatch, alveolar partial pressures of oxygen and carbon dioxide are primarily determined by inspiratory pressures and alveolar ventilation. Regions with shunt or low $\dot{V}_A/\dot{Q}$ ratios worsen arterial oxygenation while alveolar dead space and high $\dot{V}_A/\dot{Q}$ lung units lessen CO_2 elimination efficiency. Although less common, diffusion limitation might cause hypoxemia in some situations. This review covers the principles of lung gas exchange and therefore mechanisms of hypoxemia or hypercapnia. In addition, we discuss different metrics that quantify the deviation from ideal gas exchange.

Keywords

- ventilation-perfusion ratio
- respiratory dead space
- respiratory physiology
- pulmonary ventilation
- hypoxia
- hypercapnia

Oxygen (O_2) is required for cellular respiration in all multicellular organisms. In humans, the first step in delivering O_2 to the cellular level is via uptake from air through the lungs. Carbon dioxide (CO_2), the byproduct of cellular metabolism, must continuously be eliminated from the body via the lungs to maintain homeostasis. Blood carries O_2 to the tissues for metabolism and delivers CO_2 from these tissues to the lungs for elimination. Ventilation brings O_2 to the blood while concurrently removing CO_2 from the blood. Efficient respiratory gas exchange therefore requires the intimate matching between blood flow and ventilation in the lung. Clinically, most cases of impaired gas exchange are caused by a reduced correlation between regional lung ventilation and blood flow, known as $\dot{V}_A/\dot{Q}$ mismatch ($\dot{V}_A$ alveolar ventilation; $\dot{Q}$ total lung blood flow), i.e., lung regions that are either over- or under-ventilated in proportion to regional blood flow. The main part of this review will therefore discuss how different forms of $\dot{V}_A/\dot{Q}$ mismatch affect gas exchange efficiency for O_2 and CO_2. To adequately describe basic principles that are equally important in situations where $\dot{V}_A/\dot{Q}$ mismatch is present, we will start with gas exchange in an ideal lung with no $\dot{V}_A/\dot{Q}$ mismatch. Because there is only limited $\dot{V}_A/\dot{Q}$ mismatch in normal lungs, gas exchange in healthy individuals comes close to this model.

Gas Exchange in a Lung without $\dot{V}_A/\dot{Q}$ Mismatch

The active part of pulmonary uptake of O_2 is tidal breathing that brings air with a high inspiratory partial pressure of oxygen (P_IO_2) to the lung alveoli (►**Fig. 1**). When breathing air (20.9% O_2), P_IO_2 is 159 mm Hg if barometric pressure (P_B) is 760 mm Hg, often taken as normal P_B at sea level, (0.209×760 mm Hg $= 159$ mm Hg). During passage through the conducting airways, inspired gas is heated to body temperature and humidified to 100% relative humidity, corresponding to a partial pressure of water vapor (P_{H_2O}) of 47 mm Hg. The addition of water vapor dilutes inspired air,

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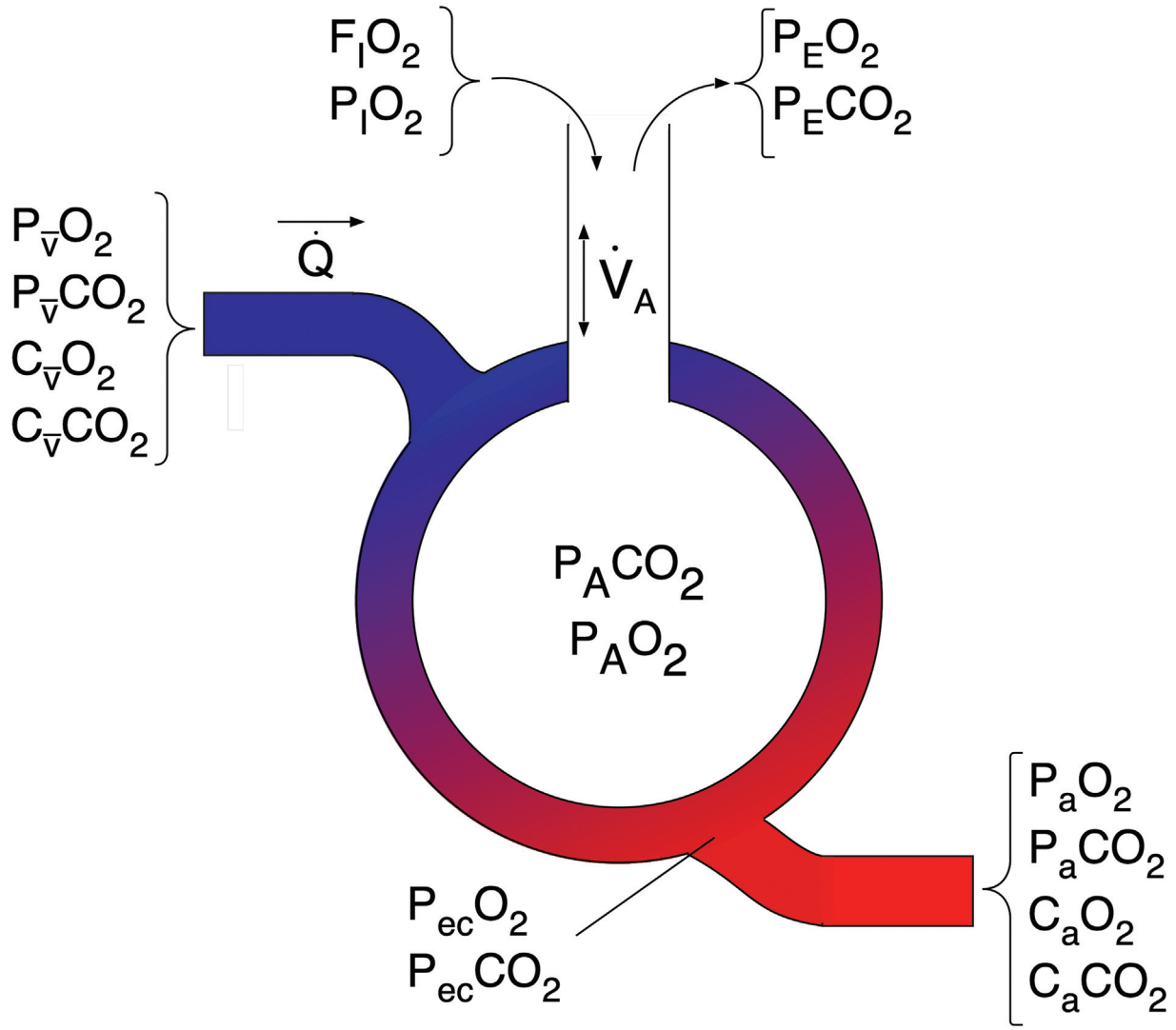

Fig. 1 Model of single alveolus (gas exchanging unit) displaying the traditional nomenclature used to describe fractions (F), partial pressures (P) and content (C) of gases (O_2 and CO_2) in venous blood (v), end-capillary blood (ec), inhaled gas (I), exhaled (E) gas, and alveolar gas (A). $\dot{Q}$ and $\dot{V}_A$ represent blood flow and ventilation, respectively.

reducing partial pressures of other inspired gases. During the conditions assumed above, PO_2 of inspired gas reaching the distal airways is therefore 149 mm Hg (0.209 × [760 mm Hg – 47 mm Hg]). Alveolar PO_2 (P_AO_2) is then further reduced by continuous uptake of O_2 from alveolar gas to blood in the alveolar capillaries. Although lower than P_IO_2, P_AO_2 is much greater than PO_2 of mixed venous blood ($P_{\bar{v}}O_2$), at rest in a normal subject ~ 40 mm Hg, entering the alveolar capillaries causing oxygen to diffuse from alveolar gas into the blood. This is a passive process driven solely by partial pressure differences as there is no active transport of O_2 across the alveolar capillary membrane. In most situations, the result is equilibration between P_AO_2 and PO_2 of end-capillary blood ($P_{ec}O_2$) leaving the alveoli (►**Fig. 1**). The diffusion and equilibration of gas partial pressures is facilitated by several structural components in the lung: (1) the exceptionally thin membrane, only 1 µm,[1,2] separates the alveolar gas and blood compartments, (2) the large surface area for gas exchange (140 $m^{2,3}$), (3) exposure of blood to several gas-exchanging units, and (4) the relatively large blood volume within the alveolar capillaries which slows blood flow, allowing more time for gas exchange (►**Fig. 2**). At rest, transit time through the alveolar capillaries is normally 0.25 to 0.75 second. In this theoretical model of a lung without $\dot{V}_A/\dot{Q}$ mismatch, P_AO_2 and hence $P_{ec}O_2$ are identical for all lung regions. Oxygenation of arterial blood is therefore primarily dependent on P_AO_2. P_AO_2 can be estimated from the ideal alveolar gas equation in which the delivery of O_2 to the alveolar compartment is represented by the first part of the equation (explained below in Box 1) and the removal of O_2 from the alveolar space is represented by the second part of the equation where the term P_aCO_2/R represents the amount of oxygen being removed.[4–6] As shown in Box 1, with a normal arterial PCO_2 (P_aCO_2) and during the conditions stated, the alveolar gas equation results in a

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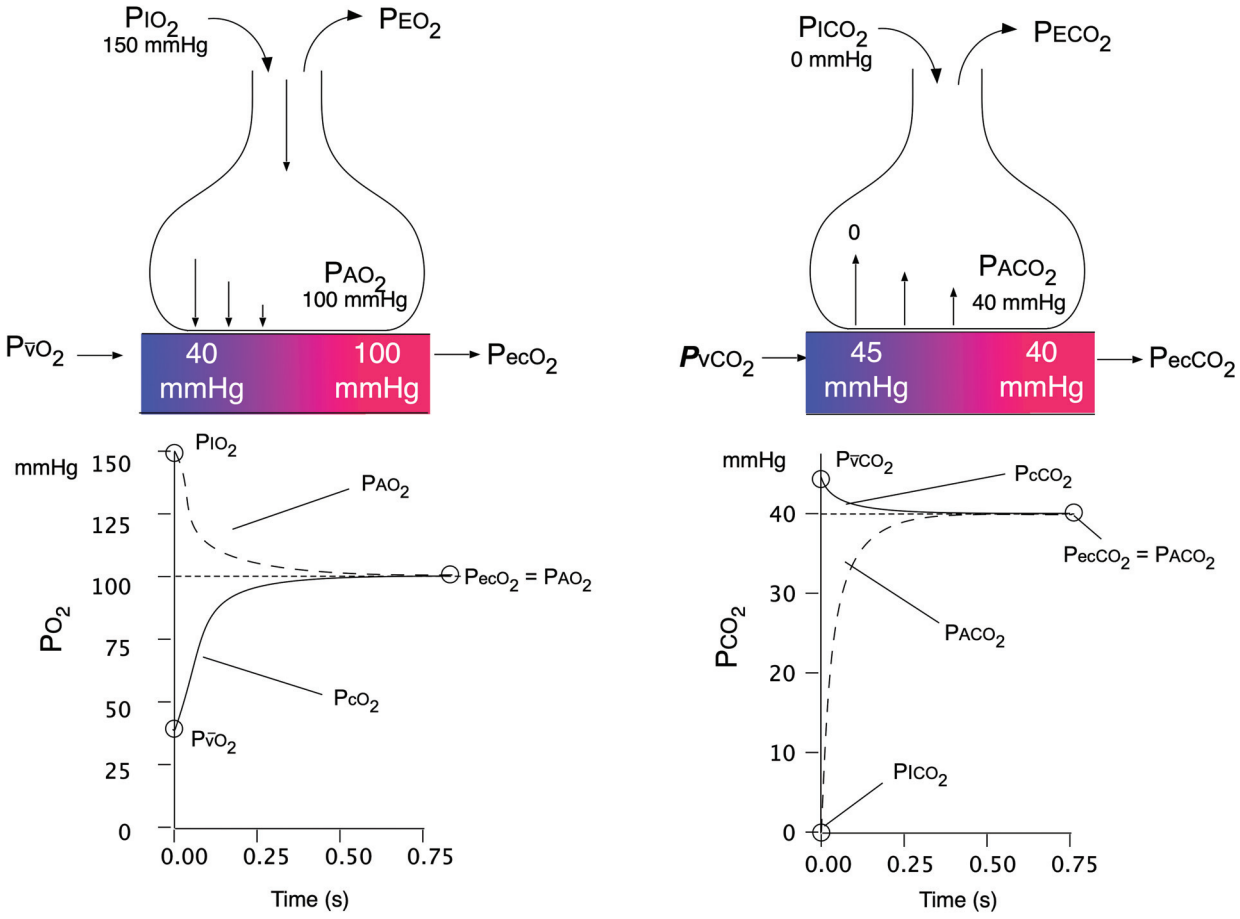

Fig. 2 Time course of PO_2 and PCO_2 as they rapidly reach equilibration through passive diffusion across the alveolar-capillary membrane. The figures demonstrate that there is no difference between the alveolar and end-capillary pressures within the time it takes for blood to traverse the gas-exchanging lung regions. At rest the normal transit time is 0.25 to 75 seconds. Notations are explained in ►**Fig. 1**.

P_AO_2 of approximately 102 mm Hg. Note that in this idealized lung model, the difference between alveolar and arterial PO_2 ($P_{A\text{-}a}O_2$) is zero. We will come back to how the $P_{A\text{-}a}O_2$ difference can be used to assess gas exchange impairment.

Elimination of carbon dioxide (CO_2) occurs in a similar manner but of course in the opposite direction. In a normal subject at rest, partial pressure of carbon dioxide in mixed venous blood ($P_{\bar{v}}O_2$) is approximately 45 mm Hg, which is greater than PCO_2 in alveolar gas (P_ACO_2; ►**Fig. 1**). CO_2 therefore diffuses from blood in the alveolar capillaries to the alveolar space. Tidal breathing eliminates alveolar gas with a high PCO_2 and replaces it with fresh gas with PCO_2 close to zero, which maintains P_ACO_2 lower than $P_{\bar{v}}O_2$ (►**Figs. 2** and **3**). The equilibration between PCO_2 in blood and alveolar gas is even more rapid than for O_2 because the resistance to diffusion is even less than for O_2. Therefore, $P_{ec}CO_2$ and P_aCO_2 become equilibrated with the P_ACO_2. As with O_2, there is no active transport of CO_2 across the alveolar capillary membrane.

We have greatly simplified the concepts of gas exchange above. With tidal breathing, P_AO_2 and P_ACO_2 will rise and fall with each breath. These fluctuations are not reflected in temporal variations in arterial gases due to differences in regional blood transit times and ventilation across the lung that act as a mixing or smoothing process. When we speak about the partial pressures of gases in various compartments, we therefore ignore any temporal fluctuations and present mean values over multiple respiratory cycles.

Delivery of O_2 to peripheral tissues and CO_2 to the lungs is covered in detail elsewhere (see Chapter 5), and depends on cardiac output, tissue perfusion, and the amount of each gas in blood. O_2 is carried in blood bound to hemoglobin (Hgb) and dissolved in plasma. Each hemoglobin molecule has four binding sites for O_2 and the affinity for each of these binding sites is influenced by several factors including the number of bound oxygen sites, P_aCO_2, pH, and temperature of the blood. The resultant hemoglobin–O_2 saturation and content curves are shown in ►**Fig. 4**. The sigmoidal shape of these curves plays an important role in O_2 uptake in the lungs and offloading of O_2 to the peripheral tissues. The amount of O_2 dissolved in plasma is relatively small and directly proportional to P_aO_2. The O_2 content of arterial blood (C_{ao_2}) is the sum of the O_2 bound to Hgb and dissolved in plasma. For a normal P_aO_2 and Hgb, there is typically around 20 mL of O_2 in

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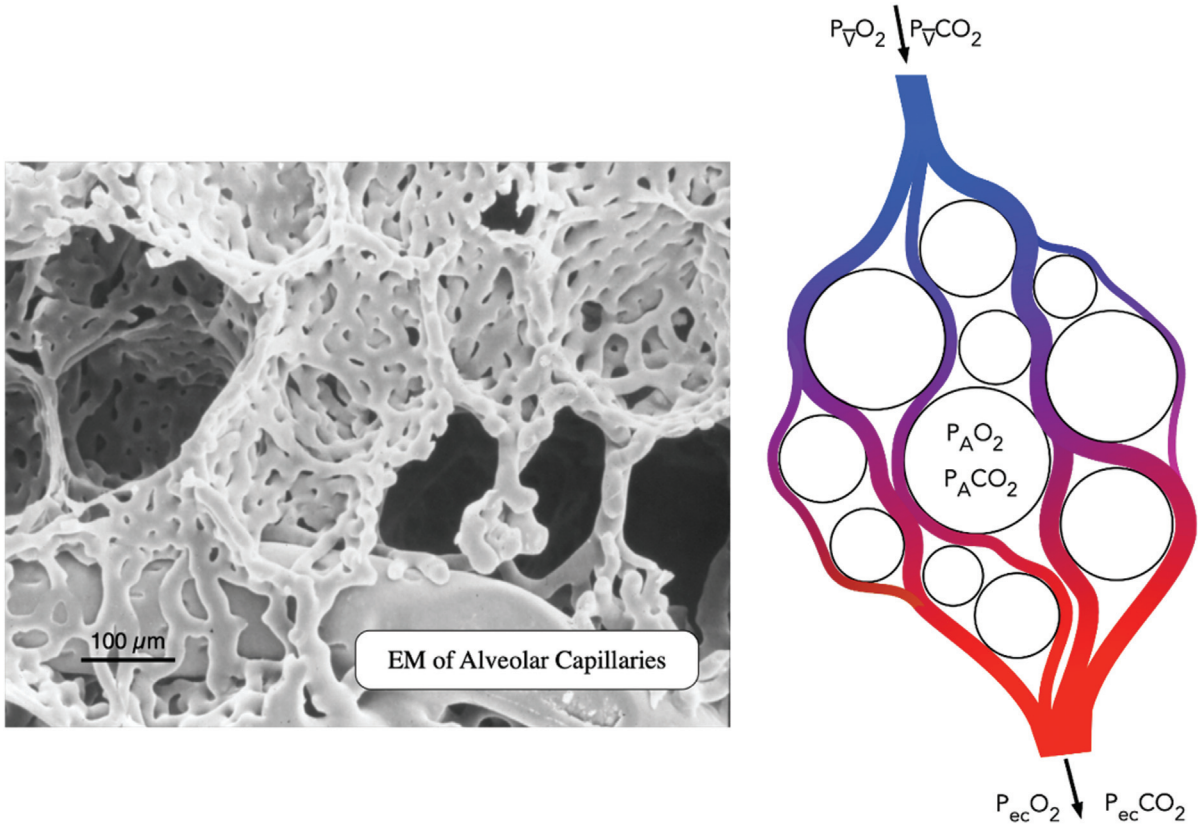

Fig. 3 Left: scanning electron micrograph of alveolar capillaries demonstrating the network of capillaries that surround the alveoli.[46] Right: schematic demonstrating the blood exchanging gas with multiple alveoli as it traverses the gas-exchanging regions in the lungs. Notations are explained in ►**Fig. 1**.

100 mL of blood (20 mL/dL). CO_2 is carried in blood bound to Hgb, as bicarbonate (HCO_3^-) and dissolved in plasma. The binding of CO_2 to hemoglobin does not change the affinity of Hgb for CO_2 as happens with O_2, resulting in a more linear relationship between P_aCO_2 and the content of CO_2 (C_{ao_2}) in blood (►**Fig. 4**). For a normal P_aCO_2 and Hgb, there is typically around 50 mL of CO_2 in 100 mL of blood (50 mL/dL). The arterial to venous content differences for O_2 and CO_2 are similar (~5 mL/dL), hence the alveolar uptake of O_2 ($\dot{V}_{O_2}$, mL/min) is approximately as much as the elimination of CO_2

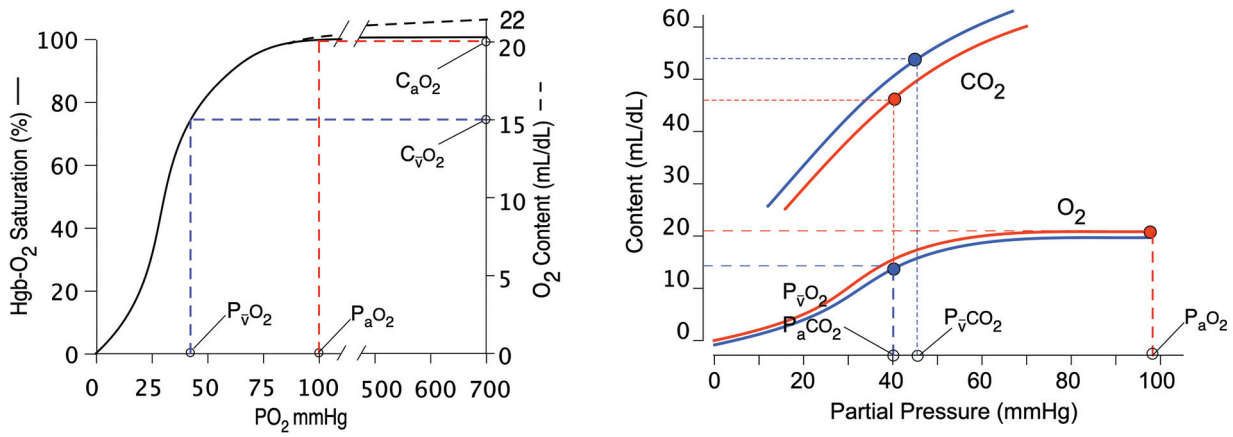

Fig. 4 Left: the hemoglobin–oxygen dissociation curve, content calculated for a hemoglobin concentration of 15 g/dL. The sigmoidal shape explains the nonlinear relationship between P_aO_2 and C_aO_2, nearly all of which is bound to hemoglobin. Note the small increase in C_aO_2 when P_aO_2 is greater than 100 mm Hg, which is one reason why high $\dot{V}_A/\dot{Q}$ regions add very little O_2 to arterial blood. Right: content of O_2 and CO_2 in blood as a function of the partial pressure of each gas in arterial (red curve) and mixed venous (blue curve). The arterial and venous curves differ in positions due to the Bohr (oxygen) and Haldane (carbon dioxide) effects. Dashed lines and markers correspond to normal values. Note the steeper curve for CO_2, the pressure difference between mixed venous and arterial blood is very different for oxygen and carbon dioxide despite very similar difference in content. Notations are explained in ►**Fig. 1**.

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($\dot{V}_{CO_2}$, mL/min), which is described by the respiratory exchange ratio ($R = \dot{V}_{CO_2}/\dot{V}_{O_2}$, also called the respiratory quotient), at steady state, 0.7 to 1.0. The different relationships between partial pressures and contents mean that the drop in PCO_2 between mixed venous and end-capillary blood is approximately 5 mm Hg, while the increase in PO_2 is approximately 60 mm Hg (►**Fig. 4**).

In summary, ventilation maintains alveolar gas with PO_2 greater and PCO_2 lower than partial pressures in the mixed venous blood. The differences in partial pressure results in diffusion of oxygen and carbon dioxide across the alveolar-capillary membrane so that, in the absence of diffusion limitation (discussed later), end-capillary partial pressures equilibrate with those in alveolar gas (►**Fig. 2**). In a model with no $\dot{V}_A/\dot{Q}$ mismatch and no diffusion limitation, P_AO_2 and P_ACO_2 are uniform across the lung and $P_{A\text{-}a}O_2$ and $P_{a\text{-}A}CO_2$ differences are zero. It is important to understand that the absence of $\dot{V}_A/\dot{Q}$ mismatch does not require a homogeneous distribution of regional ventilation and blood flow throughout the lung. Even with heterogeneous distributions, there will be no mismatch if the regional variation in $\dot{V}_A$ and $\dot{Q}$ match each other.

Box 1: The ideal alveolar gas equation

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R} = F_IO_2 \times (P_B - P_{H_2O}) - \frac{P_aCO_2}{R}$$

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R} \times [1 - F_IO_2(1 - R)]$$

Box 1 The ideal alveolar gas equation exists in several forms, two are shown here. The upper equation is often used in clinical practice. The lower, more complex, equation takes into account that the inspiratory and expiratory minute volumes differ when the respiratory exchange ratio, R, does not equal 1.0. The effect is small but dependent on F_IO_2, with a normal R of = 0.8 and $P_aCO_2 = 40$ mm Hg the difference in calculated P_AO_2 is 2 mm Hg breathing air but 10 mm Hg with $F_IO_2 = 1.0$. Derivation of the equations is well described.[4–6] The equation defines what P_AO_2 would be in all lung regions if $\dot{V}_A/\dot{Q}$, and therefore gas exchange, is homogeneous throughout the lung, with the assumption that perfect equilibrium between P_A and P_{ec} is reached across all regions.[4] The P_AO_2 given by the equation has therefore been referred to as P_AO_2 of "ideal" alveolar gas and it can be used as a reference to quantitatively estimate the impact of $\dot{V}_A/\dot{Q}$ mismatch on P_aO_2, which corresponds to the alveolar-arterial PO_2 difference ($P_{A\text{-}a}O_2$). P_IO_2: partial pressure of O_2 in inspired gas reaching the alveoli, calculated as $P_IO_2 = F_IO_2 \times (P_B - P_{H_2O})$; F_IO_2: fraction of O_2 in inspired gas; P_B: barometric pressure; P_{H_2O}: saturated vapor pressure of water at body temperature, 47 mm Hg at 37°C; R: the respiratory exchange ratio defined as the ratio between the amount of CO_2 and O_2 exchanged across the alveolar-capillary barrier. P_B must be known or estimated for the appropriate altitude; at sea level it is commonly estimated as 760 mm Hg. If not measured, R is usually assumed to be 0.8. Using these values at sea level, the fraction of O_2 in air ($F_IO_2 = 0.21$) and a normal P_aCO_2 of 40 mm Hg, the upper equation results in $P_AO_2 = 102$ mm Hg.

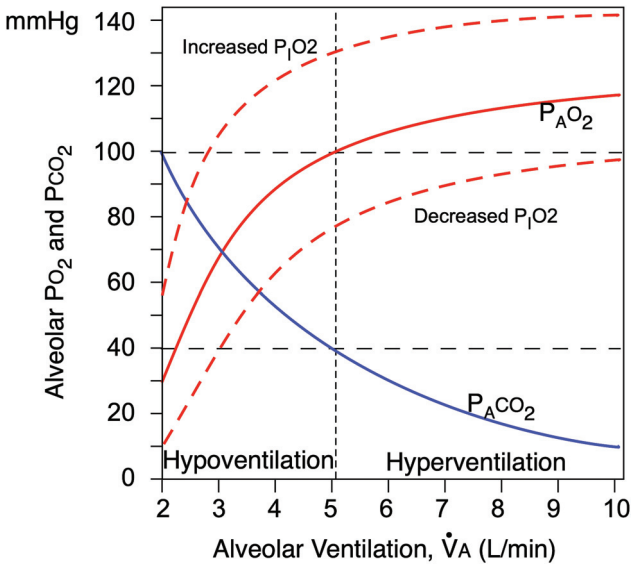

Fig. 5 Graph demonstrating the inverse relationships between P_AO_2 and P_ACO_2 as a function of alveolar ventilation. Remember that in a lung without $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation, the alveolar pressures equal P_aO_2 and P_aCO_2. Normal values for $\dot{V}_A$, P_AO_2, and P_aCO_2 are indicated by the dashed lines. The upper dashed red curve illustrates the effect of increasing F_IO_2 which raises P_IO_2. The lower dashed curve illustrates the effect of decreased P_IO_2, e.g., at high altitude. The curves are derived assuming unchanged cardiac output, O_2 consumption and CO_2 production and with mixed venous values changing with changes in P_aO_2 and P_aCO_2. For example, with hypoventilation $P_{\bar{v}}O_2$ is lower and $P_{\bar{v}}CO_2$ higher than normal. Hypoventilation results in both hypoxemia and hypercapnia. An increase in F_IO_2 results in an upward shift of the PO_2 curve while the PCO_2 curve remains fixed. An increase in $\dot{V}O_2$ and $\dot{V}_{CO_2}$ would shift the P_AO_2 curve downward and the P_ACO_2 curve upward which illustrates the corresponding changes in alveolar and arterial partial pressures if $\dot{V}_A$ remains unchanged. Notations are explained in ►**Fig. 1**.

Effects of Changes in alveolar ventilation ($\dot{V}_A/\dot{Q}$), $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$

Above we described a theoretical lung without $\dot{V}_A/\dot{Q}$ mismatch, P_AO_2 and $P_aO_2 \sim 102$ mm Hg and normal P_aCO_2 and $P_aCO_2 \sim 40$ mm Hg. By definition this also corresponds to a normal alveolar ventilation ($\dot{V}_A$; we discuss the relationship between $\dot{V}_A$ and minute ventilation ($\dot{V}_E$) later). ►**Fig. 5** illustrates how P_AO_2 and P_ACO_2 vary with $\dot{V}_A$ if $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ remain unchanged. Greater alveolar ventilation (i.e., hyperventilation) increases P_AO_2 and lowers P_ACO_2. P_aO_2 and P_aCO_2 shift accordingly because our model assumes equilibration between alveolar and capillary blood partial pressures. Lower $\dot{V}_A$ (i.e., hypoventilation) reduces P_AO_2 and P_aO_2 but increases P_ACO_2 and P_aCO_2. Hypo- and hyperventilation are here in fact defined not by minute ventilation but by P_aCO_2 being outside the normal range. The relationship between P_ACO_2, alveolar minute ventilation, and $\dot{V}_{CO_2}$ is described by the alveolar ventilation equation:

$$P_ACO_2 = K \times \frac{\dot{V}_{CO_2}}{\dot{V}_A}$$

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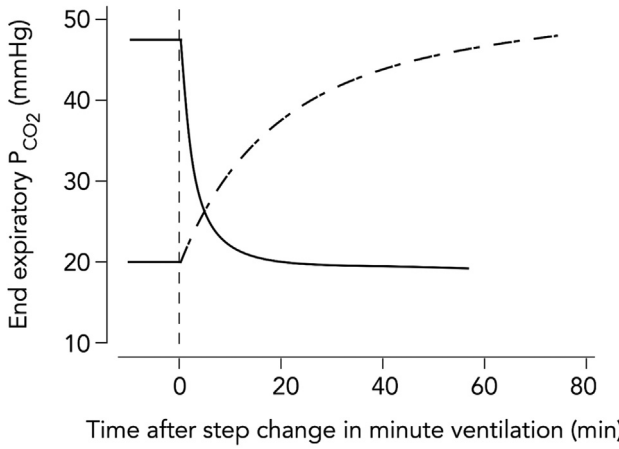

Fig. 6 Changes in P_ACO_2 (using end-expiratory CO_2 as a surrogate measure) with a step change in ventilation from 14 to 3.3 L/min (solid line) and conversely from 3.3 to 14 L/min (dashed line); P_aCO_2 follows a similar pattern. Note how much more quickly the P_ACO_2 reaches a new steady state when ventilation is increased compared with decreased because in the latter situation it takes time to build up the body stores of CO_2. For clarity the diagram illustrates a big change in ventilation, for a more realistic change the shift in partial pressure and the time course shorter. (Reproduced with permission from Lumb[21].)

where $\dot{V}_A$ refers to alveolar ventilation, the part of minute $\dot{V}_E$ that participates in gas exchange (explained further below), K is a constant (= 0.863 if P_ACO_2 in mm Hg, $\dot{V}_{CO_2}$ in mL STPD*/min, and $\dot{V}_A$ L BTPS*/min). For example, if $\dot{V}_A$ is reduced by 50% and $\dot{V}_{CO_2}$ remains unchanged, P_ACO_2 will double. This does not happen immediately, at first when $\dot{V}_A$ is reduced CO_2 *elimination* will be reduced to the same degree. The imbalance between unchanged CO_2 *production* at the cellular level but reduced elimination means that P_ACO_2 (and therefore P_aCO_2) will increase gradually until a new steady state between CO_2 production and elimination is reached at a higher P_ACO_2. Higher P_ACO_2 means that more CO_2 is eliminated per unit alveolar ventilation. Depending on gas exchange efficiency of an individual's lungs, it takes 10 to 20 minutes to reach this steady state, reflecting the time required for the body storage of CO_2 to build up to the new equilibrium (►**Fig. 6**). This time frame roughly applies to all sudden changes in $\dot{V}_A$ or $\dot{V}_{CO_2}$. Because the body stores of O_2 are much smaller than for CO_2, P_aO_2 reaches a steady state much faster after changes in $\dot{V}_A$, F_IO_2, or $\dot{V}_{O_2}$. If, instead, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are increased but $\dot{V}_A$ remains unchanged, P_AO_2 and P_aO_2 will decrease and P_ACO_2 and P_aCO_2 increase. With unchanged $\dot{V}_A$ and decreases in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, the partial pressures change in the opposite directions. Because of the respiratory control system, which maintains a constant $\dot{V}_{CO_2}/\dot{V}_A$ ratio, this does normally not correspond to a situation in a spontaneously breathing subjects. It can however be observed, for example, in a patient who is receiving neuromuscular blockade on controlled mechanical ventilation and who has a significant increase or decrease in body temperature which corresponds to an increase or decrease in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. Hypoventilation is one example of how hypoxemia might occur without any lung pathology. If we calculate the $P_{A\text{-}a}O_2$ for this situation, the difference will be zero for the ideal lung model. Even in a healthy individual, $P_{A\text{-}a}O_2$ is somewhat greater than zero, but during hypoventilation not increased compared with a situation with normal $\dot{V}_A$. This differentiates hypoxemia caused by hypoventilation from hypoxemia due to $\dot{V}_A/\dot{Q}$ mismatch (see below).

* STPD, standard temperature and pressure dry (excluding any contribution water vapor to the measured volume); BTPS, body temperature and pressure saturated (saturated meaning 100% relative humidity). BTPS is used to relate, e.g., a tidal volume to the volume it would occupy in the lungs and airways. STPD is used to relate volume or flow to the quantitative (e.g., mmol) uptake or elimination of a gas.

Effect of Changes in F_IO_2 and P_IO_2

The first term of the alveolar gas equation states that P_IO_2, and therefore F_IO_2 and P_B, are determinants of P_AO_2. For example, an increase in F_IO_2 shifts the P_AO_2 versus $\dot{V}_A$ curve in ►**Fig. 5** upward. This corresponds to the clinical situation when administration of O_2 to a patient who is hypoventilating results in increased P_aO_2. Similarly, lower P_B at a high altitude moves this curve downward, illustrating the effect of altitude on P_AO_2. This demonstrates that although the fraction of O_2 in air is always 0.21, decreasing P_B causes a proportional decrease in P_IO_2. Although the response to high altitude might include hyperventilation, which increases P_aO_2, curves for different P_B illustrate that for a certain $\dot{V}_A$, P_AO_2 and therefore P_aO_2 are reduced with a lower P_B. Again, raising F_IO_2 corresponds to an upward shift of the P_AO_2 versus $\dot{V}_A$ curve, demonstrating that administration of supplemental O_2 is an additional strategy to mitigate the effect of high altitude on P_aO_2. Remember that it is P_B and F_IO_2 that determine P_IO_2. In summary, lower P_B results in lower P_AO_2 which might lead to hypoxemia even if the lung is normal, but this is influenced by any change in $\dot{V}_A$ and F_IO_2. If $P_{A\text{-}a}O_2$ is calculated for these situations, it would again be zero if the lung is without $\dot{V}_A/\dot{Q}$ mismatch and there is no diffusion limitation (discussed next).

Diffusion Limitation

So far, we have assumed equilibration between P_A and P_{ec} for both O_2 and CO_2, which is accurate for individuals with normal lungs in most situations. In contrast, diffusion limitation refers to a situation where P_{ec} fails to fully equilibrate with P_A. Fick's law of diffusion states that the rate of net transfer of a gas ($\dot{V}_{gas}$) across the alveolar-capillary membrane by diffusion is determined by molecular size, the difference in partial pressure across the membrane (the driving pressure for diffusion, ΔP), membrane area (A), membrane thickness (T), and the solubility of the gas in the membrane:

$$\dot{V}_{gas} = D \times \Delta P \times \frac{A}{T}$$

where D is a constant referring to properties of the gas and the membrane according to

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$$D \propto \frac{S}{\sqrt{MV}}$$

S is the solubility of the gas in the membrane and MW is the molecular weight of the gas. The rate of uptake of O_2 from alveolar gas to blood per unit driving pressure (e.g., mL/min/mm Hg) is termed lung diffusing capacity for oxygen $D_{L_{O_2}}$.

$$D_{L_{O_2}} = \frac{\dot{V}_{O_2}}{\Delta P}$$

Here ΔP refers to the difference in PO_2 between alveolar gas and capillary plasma. Hemoglobin acts as an O_2 sink by rapidly binding the O_2 from the plasma, reducing PO_2, and increasing the driving pressure of O_2 from the alveolus to the blood. The pathway for oxygen includes not only the actual alveolar-capillary membrane but also the pathway through plasma to the erythrocytes. The chemical reaction when O_2 is bound to Hb takes time and this is also an important determinant for the rate of O_2 uptake. Roughton and Forster[7] showed that the resistance to diffusion of oxygen can be divided in two components in series so that

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_c}$$

D_M is the resistance to diffusion across the alveolar-capillary membrane and plasma to the erythrocytes, V_c is the blood volume in the lung capillaries, and θ is a constant describing the amount of gas taken up by the hemoglobin per unit time and unit driving pressure. The equation takes this form because diffusing capacity is analogous to conductance and resistance is the reciprocal of conductance.

As stated above, one determinant of the diffusion capacity is the area available for gas exchange. Because gas exchange will only occur in perfused alveolar regions, the area depends on both lung volume and the distribution of blood within the lung capillaries. An increased number of alveoli that are either not ventilated or not perfused decreases diffusion capacity. From this, it follows that $\dot{V}_A/\dot{Q}$ mismatch might affect diffusion capacity, which means that whole lung decreased diffusion capacity does not require diffusion limitation, defined as failure of equilibration between P_A and P_{ec}. The multiple inert gas elimination method can be used to calculate the P_aO_2 expected with the observed degree of $\dot{V}_A/\dot{Q}$ mismatch.[8] The difference between the expected and measured P_aO_2 has been used an estimate of the real effect of diffusion limitation. Using this approach in patients with idiopathic pulmonary fibrosis, Agustí et al demonstrated that 20% of the hypoxemia observed at rest could be ascribed to diffusion limitation while the remainder was due to $\dot{V}_A/\dot{Q}$ mismatch.[8] With exercise, diffusion limitation caused 40% of the observed hypoxemia. This demonstrates that, although not dominant, the properties of the alveolar-capillary membrane might be an important determinant of diffusion capacity in patients with some lung diseases. The relationship between lung volume and the surface area available for gas exchange means that diffusion capacity is maximal at total lung capacity. In diseases that cause destruction of alveoli, e.g., emphysema, reduction of the area available for gas exchange is one cause of reduced diffusion capacity. In clinical medicine, measurements of diffusion capacity for carbon monoxide or nitric oxide are used to evaluate and monitor lung function. These methods have been discussed in detail in several excellent reviews.[9,10]

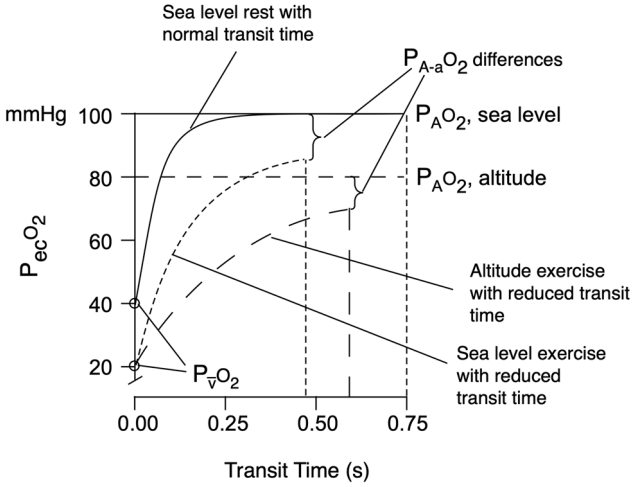

Fig. 7 Time course of capillary PO_2 as blood traverses the alveolar capillaries. At rest and sea level, there is more than enough time for the $P_{ec}O_2$ to equilibrate with the P_AO_2. With increased blood flow (decreased transit time) during exercise, there may not be enough time for the $P_{ec}O_2$ to equilibrate with the P_AO_2, i.e., diffusion limitation, resulting in an increased $P_{A\text{-}a}O_2$ difference. The lower $P_{\bar{v}}O_2$ during exercise means that more O_2 needs to be taken up by the blood to reach P_AO_2, higher altitude lowers P_AO_2 and hence the driving pressure for oxygen diffusion into the blood. Both these factors add to the tendency to diffusion limitation. Notations are explained in ►**Fig. 1**.

The solubility of CO_2 in water or tissue is approximately 30 times greater than for O_2 while the molecular weight of CO_2 is slightly greater than O_2, resulting in the resistance to diffusion across the membrane for CO_2 being roughly 20 times less than for O_2. The chemical reactions eliminating CO_2 from the blood limit the rate of CO_2 transfer from the blood to the alveolar gas so that the total resistance to diffusion between blood and alveolar gas has been estimated as roughly half of that for O_2. Diffusion limitation is therefore not of importance for the elimination of CO_2. It is also worth considering that even without equilibration between P_ACO_2 and $P_{ec}CO_2$, this would have little effect on P_aCO_2 due to the small difference between $P_{\bar{v}}CO_2$ and P_aCO_2.

►**Fig. 7** illustrates that the equilibration of $P_{ec}O_2$ with P_AO_2 depends on (1) the low resistance to diffusion with a rapid increase in $P_{ec}O_2$ to P_AO_2, (2) the transit time through the alveolar capillaries, and (3) the pressure difference between $P_{\bar{v}}O_2$ and P_AO_2, i.e., how much O_2 needs to diffuse across the alveolar-capillary membrane to reach equilibrium. Changes in these factors might result in diffusion limitation. In fact, significant hypoxemia caused by diffusion limitation is often the result of a combination of two or all three of these mechanisms. One example is increased resistance due to interstitial lung disease in combination with exercise, which decreases the transit time due to increased cardiac output and tends to reduce $P_{\bar{v}}O_2$, which in turn means that more O_2

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must be taken up by the blood to reach a $P_{ec}O_2$ that equals P_AO_2. Hypoxemia due to diffusion limitation responds nicely to supplemental O_2. Of course, this does not correct the diffusion limitation, instead increased F_IO_2 raises both P_AO_2 and P_aO_2 although $P_{A\text{-}a}O_2$ remains increased (see legend to ►**Fig. 7**).

Effect of $\dot{V}_A/\dot{Q}$ Mismatch on Gas Exchange

So far, we have discussed gas exchange in a lung without $\dot{V}_A/\dot{Q}$ mismatch. This corresponds to a model with a single gas-exchanging unit, since with just one unit there can be no mismatch. The gas exchange capacity of the lung rests however on a design with a very large number of parallel gas-exchanging units. This design creates a very large surface area for the alveolar-capillary membrane encompassed within a comparably small volume. The drawback is that gas exchange efficiency decreases if each lung region does not receive equal proportions of the total blood flow and ventilation, i.e., if regional ventilation and perfusion do not match. Note that perfect matching does not require uniform distributions of regional ventilation and perfusion but it does require that regions that receive a lower fraction of total ventilation also receive an equally lower fraction of total blood flow, and that a region that receives a greater fraction of total blood flow also receives a greater fraction of total ventilation. Perfect matching thus means that the $\dot{V}_A/\dot{Q}$ ratio is uniform across all lung regions. Conversely, if the ratio varies between regions there is $\dot{V}_A/\dot{Q}$ mismatch, which causes P_aO_2 to be lower and P_aCO_2 to be higher than they would have been with perfect matching and other conditions unchanged. $\dot{V}_A$ and $\dot{Q}$ are usually of the same magnitude, approximately 5 L/min in a normal individual at rest. This means that the global $\dot{V}_A/\dot{Q}$ ratio is 1.0, and in the situation of perfect $\dot{V}_A/\dot{Q}$ match it means that the $\dot{V}_A/\dot{Q}$ ratio is 1.0 in all lung regions.

$\dot{V}_A/\dot{Q}$ Mismatch in the Normal Lung

Regional ventilation and perfusion are in fact not uniform in the normal lung. This has been ascribed to the influence of lung structure and the effect of gravity on regional lung compliance and vascular pressures.[11–15] The traditional model[14] is based on the observations that both regional ventilation and perfusion increase in the direction of gravity in upright subjects. The increase in perfusion is greater than for ventilation with $\dot{V}_A/\dot{Q}$ ratios, therefore decreasing down the lung. Higher resolution measurements used in animal studies have shown heterogeneous perfusion within iso-gravitational planes,[12] which cannot be explained by the influence of gravity. A fractal model has been suggested in which perfusion heterogeneity is explained by asymmetries in the vascular tree.[16,17] Regional ventilation and perfusion are influenced by lung volume, posture, and positive airway pressures among other factors.[12,13,18] Despite heterogeneous ventilation and perfusion, gas exchange is efficient due to the close matching of ventilation and perfusion, which has been explained by the shared influence of structure and gravity.[11] Even so, the matching is not perfect, $\dot{V}_A/\dot{Q}$ ratios, P_AO_2, and P_ACO_2 vary between regions (►**Fig. 8**) even in normal individuals.[11,19] In young normal individuals, ventilation and perfusion are mostly distributed to regions with $\dot{V}_A/\dot{Q}$ ratios between 0.3 and 2.0,[20] which corresponds to an approximate P_AO_2 range between 90 and 130 mm Hg.[19] With aging, the range of $\dot{V}_A/\dot{Q}$ ratios increases even in healthy

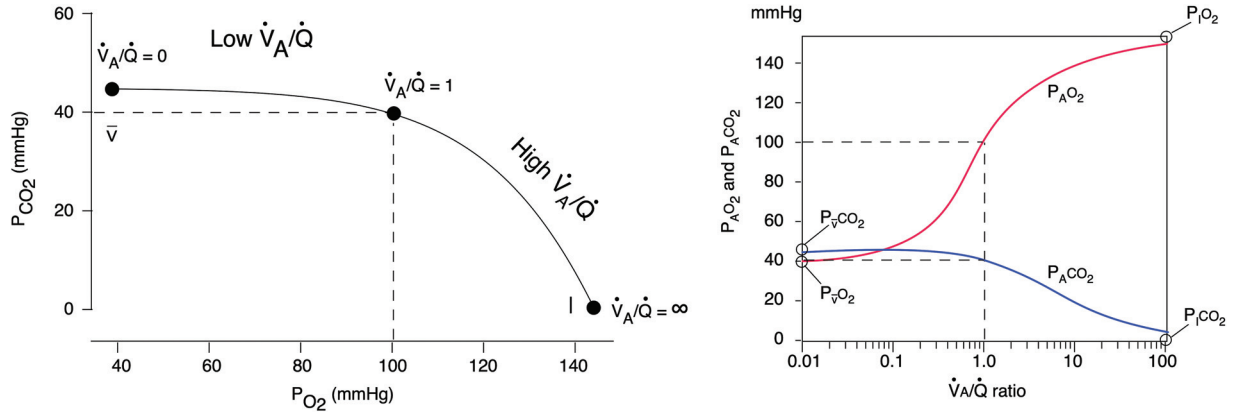

Fig. 8 Left: the classical O_2–CO_2 diagram,[41,47] showing the relationships between PO_2, PCO_2, and the $\dot{V}_A/\dot{Q}$ ratio. Right: a different representation of P_AO_2 and P_ACO_2 as determined by the $\dot{V}_A/\dot{Q}$ ratio. Both diagrams show the possible different combinations of alveolar PO_2 and PCO_2 and how these may vary across lung regions depending on their $\dot{V}_A/\dot{Q}$ ratio. Curves are constructed assuming normal values for P_IO_2, P_ICO_2 (the rightmost extremes, P_ICO_2 assumed to be zero), $P_{\bar{v}}O_2$, and $P_{\bar{v}}CO_2$(the leftmost extremes). These assumptions are not realistic for a whole lung because changes in P_aO_2 and P_aCO_2 will cause secondary changes in mixed venous values (►**Fig. 6** is more realistic in this regard), but the diagrams illustrate the influence of the $\dot{V}_A/\dot{Q}$ ratio on alveolar pressures for regional lung units in a situation when total ventilation to blood flow is sufficient to maintain normal mixed venous values. Other values for these parameters would reposition the extremes of the curves but the shape would remain similar. Starting at $\dot{V}_A/\dot{Q} = 1$, which also corresponds to the P_AO_2 given by the ideal alveolar gas equation (Box 1), moving left toward illustrates the effect of a decreasing $\dot{V}_A/\dot{Q}$ ratio on P_AO_2 and P_ACO_2. Perfusion in excess of ventilation results in a sharp decrease in P_AO_2 but much less increase in P_ACO_2. The extremes to the left correspond to a shunt ($\dot{V}_A/\dot{Q} = 0$) with alveolar PO_2 and PCO_2 identical to those in mixed venous blood. In contrast, $\dot{V}_A/\dot{Q} > 1$ results in an increase in PO_2 and a decrease in PCO_2, approaching the inspired values at the rightmost extremes, which correspond to a lung region with $\dot{V}_A/\dot{Q} = \infty$, i.e., alveolar dead space. Notations are explained in ►**Fig. 1**.

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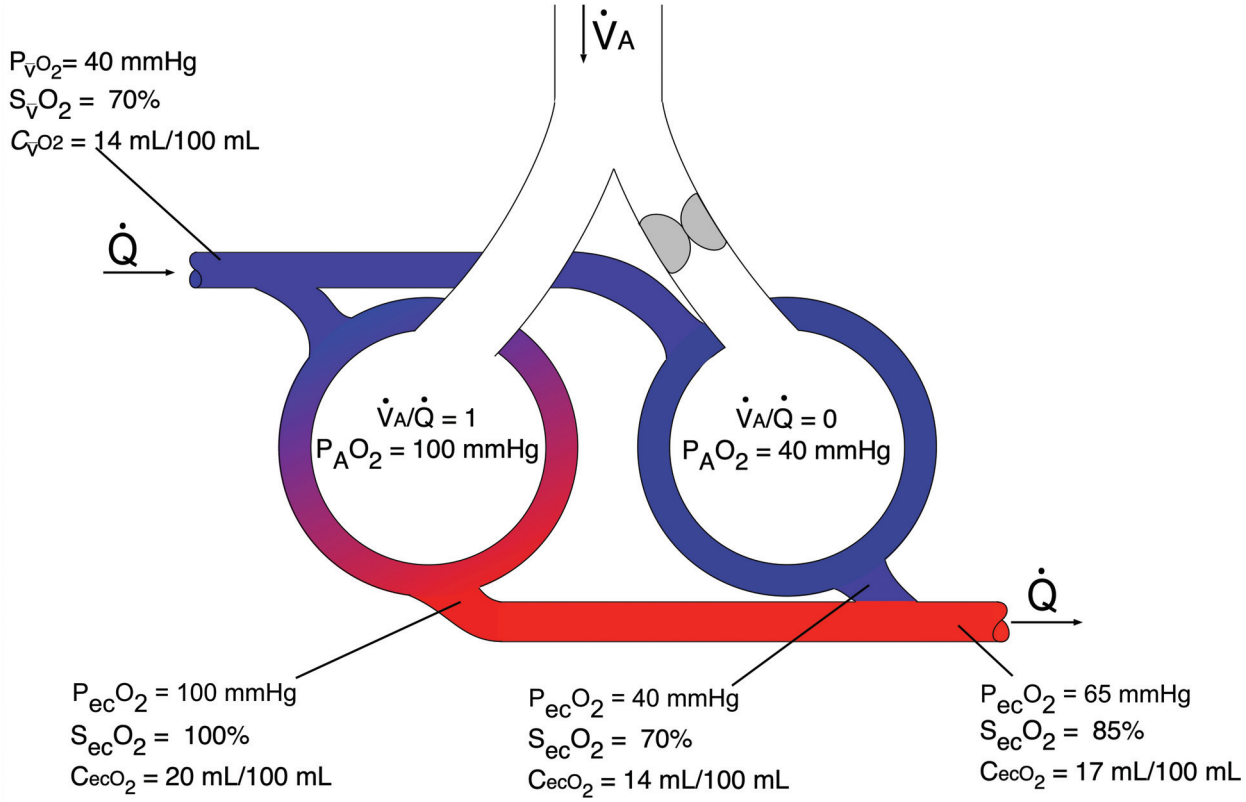

Fig. 9 Shunt illustrated by a lung model with two units, blood flow is equal for the two units but one is entirely without ventilation which constitutes a shunt, $\dot{V}_A/\dot{Q} = 0$. Because there is no gas exchange, the end-capillary partial pressures for the shunt equal those in mixed venous blood. C_aO_2 is the flow-weighted average of the content for blood from both units. The corresponding P_aO_2 is determined by the hemoglobin–oxygen dissociation curve, here calculated assuming a hemoglobin concentration of 15 g/dL. S_{ec}, end-capillary hemoglobin oxygen saturation; other notations are explained in ►**Fig. 1**.

individuals. For example, increasing airway closure causes reduced ventilation of dependent lung regions resulting in more perfusion being distributed to low $\dot{V}_A/\dot{Q}$ regions.[21,22] The result is that normal P_aO_2 decreases and normal $P_{A\text{-}a}O_2$ increases with advancing age.

Effect of Shunt on Gas Exchange

End-capillary blood from a lung region without ventilation ($\dot{V}_A/\dot{Q} = 0$) will have the same $P_{ec}O_2$ and $P_{ec}CO_2$ as mixed venous blood, which will decrease PO_2 of arterial blood (►**Fig. 9**). Quantitatively, the effect of blood from lung regions with different $\dot{V}_A/\dot{Q}$ ratios is determined by end-capillary blood O_2 content ($C_{ec}O_2$) rather than $P_{ec}O_2$. Arterial O_2 content (C_aO_2) is the flow-weighted average of blood from all lung regions (►**Fig. 9**). Shunt can be quantified as the fraction of total lung blood flow (Q_s/Q_t) that is distributed to nonventilated lung regions. The effect of shunt on P_aO_2 depends on this fraction and the O_2 content of mixed venous blood ($C_{\bar{v}}O_2$). For example, in a normal lung with $PecO_2 = 100$ mm Hg ($CecO_2 = 20.4$ mL/dL), a 20% shunt will reduce P_aO_2 to approximately 70 mm Hg ($CecO_2 = 19.3$ mL/dL) with a normal Hgb and $P_{\bar{v}}O_2 = 40$ mm Hg ($C_{\bar{v}}O_2 = 15$ mL/dL). A $P_{\bar{v}}O_2$ of 27 mm Hg ($C_{\bar{v}}O_2 = 10$ mL/dL) would result in a PaO_2 of 55 (mm Hg). Thus, for a certain Q_s/Q_t, lower $C_{\bar{v}}O_2$ results in lower P_aO_2 and conversely higher $C_{\bar{v}}O_2$ results in higher P_aO_2. In the presence of a large shunt, P_aO_2 might improve with interventions that increase $C_{\bar{v}}O_2$, e.g., increasing cardiac output or hemoglobin concentration, or decreasing $\dot{V}_{O_2}$. However, it has been demonstrated that Q_s/Q_t may increase with increasing cardiac output, which will mitigate the benefit of increased blood flow.[23,24] Increased $P_{\bar{v}}O_2$ and pulmonary arterial pressure, counteracting hypoxic vasoconstriction, have been speculated to explain the effect of cardiac output on shunt.

With increasing Q_s/Q_t, raising F_IO_2 is progressively less effective in improving P_aO_2. An F_IO_2 of 1.0 has only a small effect on P_aO_2 if there is a large shunt fraction, which is illustrated by the iso-shunt diagram (►**Fig. 10**). The explanation for this is twofold, (1) increased F_IO_2 cannot improve P_AO_2 in unventilated regions and (2) little O_2 can be added to blood-perfusing regions with a normal, or increased, $\dot{V}_A/\dot{Q}$ ratio because the blood in these regions is already fully saturated with O_2. The effect of raised F_IO_2 is however different for regions with a $\dot{V}_A/\dot{Q}$ ratio that is low but >0, see below. An extrapulmonary right-to-left shunt has the same effect on P_aO_2 as an intrapulmonary shunt. In normal individuals, venous blood from bronchial and Thebesian veins is combined with arterial blood in an amount corresponding to a shunt of 2 to 3%.[21] This is one of the mechanisms causing the normal $P_{A\text{-}a}O_2$ difference to be greater than 0, the other being the small $\dot{V}_A/\dot{Q}$ mismatch in normal lungs. The effect of shunt on CO_2 elimination is discussed below.

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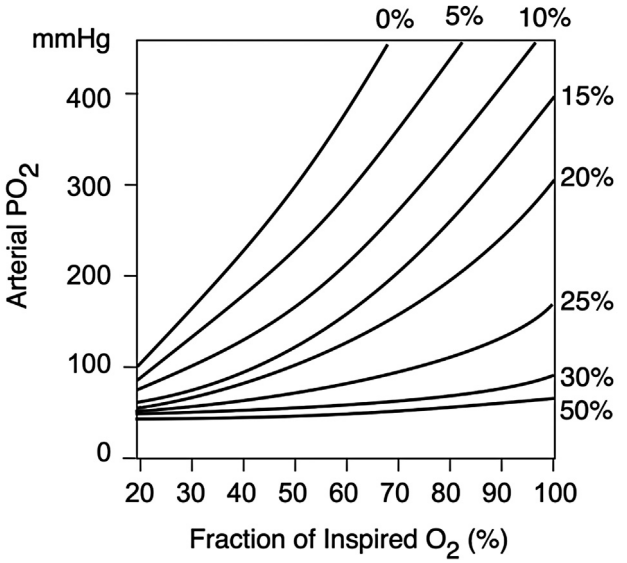

Fig. 10 The iso-shunt diagram which illustrates the theoretical relationship between F_IO_2 and P_aO_2 with shunt corresponding to different percentages of cardiac output. With no shunt, PaO_2 increases almost linearly with F_IO_2, with increasing shunt the response is increasingly less. That is, with a large shunt, increasing F_IO_2 has limited to almost no effect on P_aO_2. Modelling is based on an arterial-mixed venous oxygen content difference of 5 mL/dL and a hemoglobin concentration of 14 g/dL. (Modified from Benatar et al[48])

Effect of Low $\dot{V}_A/\dot{Q}$ Regions on Gas Exchange

Although shunt regions correspond to regions with the lowest possible $\dot{V}_A/\dot{Q}$ ratio, the term "low $\dot{V}_A/\dot{Q}$ region" often refers to regions with perfusion out of proportion to ventilation, but with $\dot{V}_A/\dot{Q} > 0$. ►**Fig. 8** shows that P_AO_2 and $P_{ec}O_2$ for these regions decrease progressively with lower $\dot{V}_A/\dot{Q}$ ratios. The effect on P_aO_2 is thus similar to that for a shunt, but weaker. Note that even a ratio of 0.5 results in substantially lower P_AO_2 than a ratio of 1.0, which emphasizes the effect of $\dot{V}_A/\dot{Q}$ mismatching on gas exchange efficiency. The effect on P_ACO_2 is less, which is clearly shown in ►**Fig. 8**. Note the part of the curve that corresponds to low $\dot{V}_A/\dot{Q}$ is almost horizontal and a substantial drop in P_AO_2 corresponds to a small increase in P_ACO_2. The reason for this is the much smaller difference between $P_{\bar{v}}CO_2$ and P_ACO_2 than between $P_{\bar{v}}O_2$ and P_AO_2; note that the extremes of the curves to the left correspond to $P_{\bar{v}}CO_2$ and $P_{\bar{v}}O_2$. Because low $\dot{V}_A/\dot{Q}$ regions are in fact ventilated, increasing F_IO_2 is comparatively effective in raising P_aO_2 (►**Fig. 5**). Consequently, low $\dot{V}_A/\dot{Q}$ cannot be the dominant cause of low P_aO_2 in a patient whose P_aO_2 does not increase significantly with the addition of supplemental O_2.

Effect of Increased Dead Space

Anatomical dead space is that part of each inspired tidal volume that is retained in the conducting airways and consequently fails to participate in gas exchange. This volume is approximately 150 mL (2–3 mL/kg predicted body weight) or 1/3 of a normal tidal volume.[21,25] The normal dead space fraction of the tidal volume is thus approximately 0.3. A lung region that is ventilated but lacks perfusion ($\dot{V}_A/\dot{Q} = \infty$) influences gas exchange in a way similar to the anatomical dead space and is therefore called alveolar dead space. The term "apparatus dead space" refers to the volume of any equipment, e.g., a face mask or tubing, that functions as an extension of the anatomical dead space. Total dead space (V_D) is the sum of anatomical dead space and any alveolar or apparatus dead space. Total dead space can be used to divide the minute ventilation (total volume expired per minute, $\dot{V}_E$) into one part that participates in gas exchange (alveolar ventilation, $\dot{V}_A$) and dead space ventilation ($\dot{V}_D$), which does not contribute to gas exchange. Thus

$$\dot{V}_A = \dot{V}_E - \dot{V}_D$$

which can be written as

$$\dot{V}_A = \dot{V}_E \times \left(1 - \frac{V_D}{V_T}\right)$$

where V_D/V_T is the total dead space as a fraction of the tidal volume. V_D/V_T therefore expresses the fraction of minute ventilation that does not contribute to gas exchange. Note that effective ventilation, and therefore CO_2 elimination, is determined by both $\dot{V}_E$ and V_D/V_T. For example, increased V_D/V_T means that greater $\dot{V}_E$ is necessary to maintain effective alveolar ventilation adequate for a normal P_aCO_2. It is important to understand that the control of breathing usually maintains P_aCO_2 at a constant level, the primary consequence of increased V_D/V_T is thus increased $\dot{V}_E$ and work of breathing. Increased V_D/V_T results in increased P_aCO_2 and decreased P_aO_2 when $\dot{V}_E$ is not sufficiently increased due to inability to do so or in a situation where $\dot{V}_E$ is not controlled by the respiratory center. This is illustrated by ►**Fig. 5**. Note that the horizontal axis shows $\dot{V}_A$, not $\dot{V}_E$, an increase in V_D/V_T with unchanged $\dot{V}_E$ corresponds to a shift to the left (decreased $\dot{V}_A$), and a subsequent increase in $\dot{V}_E$ (increasing $\dot{V}_A$ back to the original value) will result in a shift to the right, lowering P_aCO_2 back to the original level. Also note that if V_D/V_T increases from 0.3 to, for example, 0.6, $\dot{V}_A$ decreases from 4.2 to 2.4, which would have a large effect on P_AO_2 and P_ACO_2. Maintaining a normal P_aCO_2 in this situation would require an increase in $\dot{V}_E$ from 6 to 10.5 L/min.

Effect of Low $\dot{V}_A/\dot{Q}$ Regions on Gas Exchange

High $\dot{V}_A/\dot{Q}$ refers to regions that are overventilated in proportion to perfusion but not totally without blood flow. Ventilation in excess of perfusion influences gas exchange similarly to alveolar dead space. ►**Fig. 8** shows that a progressive increase in $\dot{V}_A/\dot{Q}$ ratio results in both P_AO_2 and P_ACO_2 moving toward P_IO_2 and P_ICO_2. Lower P_ACO_2 means that less CO_2 is removed by ventilation of a high $\dot{V}_A/\dot{Q}$ region than for a region with perfusion in proportion to ventilation. High $\dot{V}_A/\dot{Q}$ regions therefore mean that a greater $\dot{V}_E$ is needed to maintain adequate CO_2 elimination but, depending on the actual $\dot{V}_A/\dot{Q}$ ratio, the effect is less pronounced than for a region with $\dot{V}_A/\dot{Q} = \infty$. ►**Fig. 8** also shows that high $\dot{V}_A/\dot{Q}$ regions have a high P_AO_2 but for two reasons this has limited effect on P_aO_2. First, by definition the contribution from these regions to total blood flow is small. Second, even with a normal P_AO_2, $P_{ec}O_2$ corresponds to nearly complete oxygen

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saturation of hemoglobin and increased P_AO_2, therefore adds little oxygen content to the end-capillary blood (►**Fig. 4**). Hence high $\dot{V}_A/\dot{Q}$ regions cannot compensate for the hypoxemia caused by low $\dot{V}_A/\dot{Q}$ regions. In contrast, however, because the CO_2 dissociation curve is linear (does not plateau), increasing high $\dot{V}_A/\dot{Q}$ regions can compensate for the inefficient CO_2 removal of low $\dot{V}_A/\dot{Q}$ regions.

The Overall Effect of $\dot{V}_A/\dot{Q}$ Mismatch

We started with a discussion of gas exchange in a lung without $\dot{V}_A/\dot{Q}$ mismatch. When there is $\dot{V}_A/\dot{Q}$ mismatch and fixed minute ventilation, there must be regions with both low and high $\dot{V}_A/\dot{Q}$ ratios relative to total lung ventilation and blood flow. If one region receives perfusion in excess of ventilation, another region must be ventilated out of proportion to perfusion. The content of O_2 and CO_2 in arterial blood is the flow-weighted average of the content of end-capillary blood from all lung regions. Low $\dot{V}_A/\dot{Q}$ regions inherently make a larger contribution to the total flow, which cause P_aO_2 to be lower than it would have been in the absence of $\dot{V}_A/\dot{Q}$ mismatch. How much lower depends on the actual $\dot{V}_A/\dot{Q}$ ratio and the fraction of total blood flow that perfuses shunt and low $\dot{V}_A/\dot{Q}$ regions. This is the reason why low $\dot{V}_A/\dot{Q}$ regions increase the $P_{A\text{-}a}O_2$ difference even in the absence of diffusion limitation. Alveolar dead space and high $\dot{V}_A/\dot{Q}$ regions make a larger contribution to expired gas, which causes CO_2 content in expired gas to be lower, and CO_2 elimination less efficient than it would have been without $\dot{V}_A/\dot{Q}$ mismatch. It is more difficult to discern the effect of $\dot{V}_A/\dot{Q}$ mismatch on CO_2 elimination than the effect on P_aO_2. One reason is that the numerical changes in PCO_2 are much smaller than for PO_2, but more importantly the effect of inefficient CO_2 elimination on P_aCO_2 is often counteracted by an increase in $\dot{V}_E$ due to sensitivity of central chemoreceptors to any increase in PCO_2. This explains why patients with lung disease causing $\dot{V}_A/\dot{Q}$ mismatch so often have a low P_aO_2 in combination with a normal P_aCO_2. High $\dot{V}_A/\dot{Q}$ regions might thus be reflected by increased P_aCO_2, increased $\dot{V}_E$, or a combination of both. As explained above, high $\dot{V}_A/\dot{Q}$ regions have little effect on P_aO_2. In summary, $\dot{V}_A/\dot{Q}$ mismatch always results in reduced gas exchange efficiency. For a fixed F_IO_2 and $\dot{V}_E$, greater mismatch always results in lower P_aO_2 and higher P_aCO_2 but the effect on P_aCO_2 is in fact often attenuated or eliminated by an increase in $\dot{V}_E$

Quantitative Estimates of $\dot{V}_A/\dot{Q}$ Mismatch

The effect of $\dot{V}_A/\dot{Q}$ mismatch on O_2 and CO_2 exchange in the lung can be quantified using the "three-compartment model" suggested by Riley and Cournand[4] (►**Fig. 11**). In this model, the lungs consist of only three compartments with different $\dot{V}_A/\dot{Q}$ ratios. One compartment with uniform, ideal, $\dot{V}_A/\dot{Q}$ matching where all gas exchange occurs, one with blood flow and no ventilation ($\dot{V}_A/\dot{Q} = 0$, shunt), and one with ventilation without blood flow ($\dot{V}_A/\dot{Q} = \infty$, dead space) (►**Fig. 11**). The model estimates the effect of $\dot{V}_A/\dot{Q}$ mismatch on P_aO_2 as venous admixture, i.e., as the percentage of cardiac output directed to the compartment with $\dot{V}_A/\dot{Q} = 0$. The

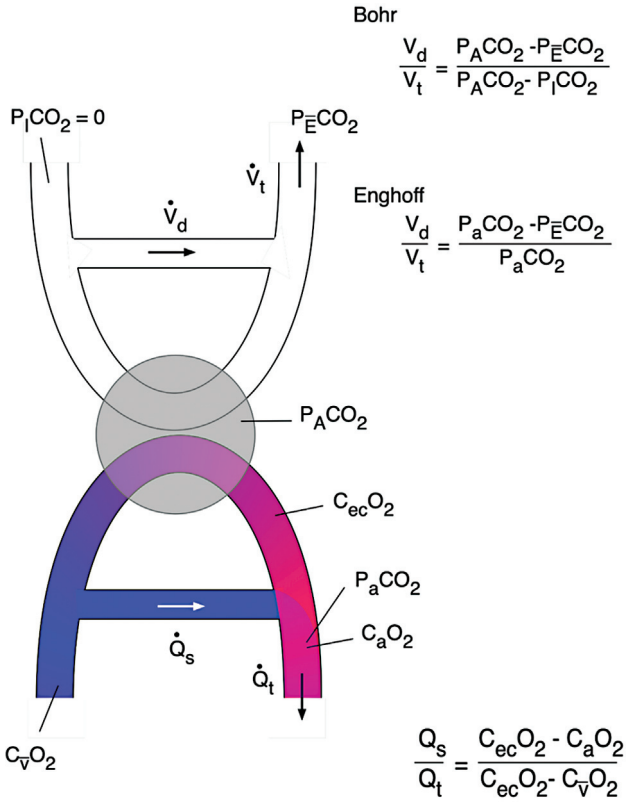

Fig. 11 An illustration of Riley and Cournand's three compartment model.[4] The Bohr, Enghoff, and shunt equations are explained in Boxes 2 and 3. Note that with this model all gas exchange is assumed to occur in one compartment with perfect $\dot{V}_A/\dot{Q}$ match. Vd, dead space volume; Vt, tidal volume; Qs, shunt blood flow; Qt, total lung blood flow. The remaining notations are explained in ►**Fig. 1**.

effect on CO_2 elimination is estimated as wasted ventilation, the fraction of $\dot{V}_E$ that ventilates the compartment with $\dot{V}_A/\dot{Q} = \infty$.

Venous Admixture

Venous admixture is calculated using the "shunt equation" (Box 2), which calculates the right-to-left shunt of mixed venous blood that would result in the observed P_aO_2. Remember that the model assumes only three $\dot{V}_A/\dot{Q}$ regions, and the venous admixture compartment must account for all of the observed hypoxemia, lumping together both low $\dot{V}_A/\dot{Q}$ and shunt. Hence the shunt equation provides an estimate of venous admixture even in the absence of true shunt (regions with $\dot{V}_A/\dot{Q} = 0$). Venous admixture is sometimes called physiologic shunt, which gives the name to the equation. We prefer the term venous admixture because this is not a measure of true shunt and also because "physiologic shunt" might be misunderstood as referring to the small amount of right-to-left shunt in normal individuals. Calculating venous admixture for values obtained when breathing 100% O_2 does provide an estimate of true shunt because in this situation the P_AO_2 in low $\dot{V}_A/\dot{Q}$ regions is so high that they have no effect on P_aO_2.[21] This approach to estimate true shunt is compromised by the tendency of breathing 100% O_2 to cause absorption atelectasis, which increases shunt. True shunt can also be measured using inert gases with very low solubility in

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blood.[19,26] The low solubility means that these gases are eliminated effectively even in regions with low $\dot{V}_A/\dot{Q}$ ratios. Any retention of the gas in arterial blood after intravenous administration is therefore an estimate of the fraction of lung blood flow through regions without ventilation. Off note, in contrast with venous admixture, using inert gas also excludes the effect of venous blood added to arterial blood by Thebesian and bronchial veins.

Wasted Ventilation

Wasted ventilation, also called physiological dead space, is calculated with the physiologic dead space equation (also known as the Bohr equation, ox 3), which estimates the total dead space ventilation, as a fraction of total $\dot{V}_E$, that would cause the observed efficiency of CO_2 elimination. Remember that this fraction is identical to the total dead space to tidal volume ratio (V_D/V_T) and that effective alveolar ventilation can be described as $\dot{V}_A = \dot{V}_E \times (1 - V_D/V_T)$. We prefer to use the term wasted ventilation as it better describes the meaning of this "as if" measure. In normal individuals wasted ventilation is close to the anatomical dead space fraction of tidal volume but the wasted ventilation includes the effect any apparatus or alveolar dead space and the effect of high $\dot{V}_A/\dot{Q}$ if present. Wasted ventilation can be viewed as a measure of the effect of $\dot{V}_A/\dot{Q}$ mismatch on the minute ventilation needed to maintain normal gas exchange. In a normal individual wasted ventilation, V_D/V_T is roughly 0.3, which means that a $\dot{V}_E = 7.5$ L/min results in $\dot{V}_A = 5.25$ L/min. In severe chronic lung disease, V_D/V_T might be in the order of 0.6[27] and in severe, acute respiratory failure, V_D/V_T might exceed 0.8, which means that a $\dot{V}_E > 25$ L/min is required to reach an effective alveolar ventilation of 5. 25 L/min.[28–30] Blood from shunt regions will have the same $P_{ec}CO_2$ as mixed venous blood which raises both P_aCO_2 and the calculated wasted ventilation, which has been coined shunt dead space.[24] The effect of shunt on the calculated wasted ventilation is an effect of using P_aCO_2 as a surrogate for P_ACO_2 according to the Enghoff modification of the Bohr equation (Box 3).[31] Although not an effect of alveolar dead space or high $\dot{V}_A/\dot{Q}$ regions, "shunt dead space" also represents impaired CO_2 elimination due to $\dot{V}_A/\dot{Q}$ mismatch.

Box 2: The shunt equation

$$\frac{Q_s}{Q_t} = \frac{C_{ec}O_2 - C_aO_2}{C_{ec}O_2 - C_{\bar{v}}O_2}$$

Box 2 Q_s/Q_t is the venous admixture quantified in the three-compartment model, expressed as the fraction of the total lung blood flow (Q_t, cardiac output) that reaches the systemic circulation without exchanging any gas. C_aO_2, $C_{\bar{v}}O_2$, and $C_{ec}O_2$ are the oxygen content of arterial, mixed venous, and end-capillary blood, respectively. C_aO_2 and $C_{\bar{v}}O_2$ are obtained from blood samples while $C_{ec}O_2$ is derived assuming that $P_{ec}O_2$ equals the P_AO_2 calculated by the ideal alveolar gas equation and the oxygen saturation of Hgb is obtained from the O_2–Hgb dissociation curve.

Box 3: Physiological dead space (Bohr–Enghoff) equation

$$\frac{V_D}{V_T} = \frac{P_aCO_2 - P_{\bar{E}}CO_2}{PaCO_2}$$

Box 3 V_D is the physiological dead space or wasted ventilation in the three-compartment model expressed as a fraction of tidal volume (V_T). The equation is derived from mass balance calculations which use the alveolar partial pressure of carbon dioxide (P_ACO_2), which is here replaced with P_aCO_2 (the Enghoff modification of the original Bohr equation[31]). In normal individuals the expired gas (P_ACO_2) from the gas-exchanging compartment is diluted by gas from the anatomical dead space which lowers the PCO_2 of mixed expired gas ($P_{\bar{E}}CO_2$), and in situations with additional alveolar or apparatus dead space $P_{\bar{E}}CO_2$, is reduced further. The difference between P_aCO_2 (the surrogate for P_aCO_2) and P_aCO_2 (divided by $P_{\bar{E}}CO_2$) is therefore proportional to the dead space fraction of total ventilation.

Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction (HPV) is precapillary vasoconstriction in lung regions with low P_AO_2, approximately <60 mm Hg. The effect is that blood flow is diverted from regions with low or no ventilation toward better ventilated regions, i.e., regions with a higher P_AO_2, which improves $\dot{V}_A/\dot{Q}$ matching and therefore P_aO_2. For example, in humans HPV reduces blood flow to atelectatic regions by up to 50%.[32,33] The beneficial effect on P_aO_2 from a similar reduction in shunt can be read from the iso-shunt diagram (►**Fig. 8**). One important aspect of HPV is that the beneficial effect on P_aO_2 decreases with the extent of the hypoxic lung regions, i.e., when the fraction of the lung vasculature with vasoconstriction increases. If we assume similarly low P_AO_2 and similar vasoconstriction in all regions (the latter is not necessarily true even with uniformly low P_AO_2), there will be no redistribution of blood flow. In this situation the consequence of HPV will be increased pulmonary vascular resistance (PVR) and increased pulmonary arterial pressure. There is therefore an inverse relationship between the proportion of lung that is hypoxic and the effect of HPV on P_aO_2; conversely, the effect of HPV on PVR is proportional to the amount of lung with low P_AO_2. Two examples of pathologic responses to global alveolar hypoxia are obstructive sleep apnea and living at high altitude, which can both present with right heart failure due to increased PVR. Animal and human experiments suggest that HPV does not contribute to the $\dot{V}_A/\dot{Q}$ matching in normal lungs.[34–36] The importance of HPV is greater in patients with disease causing regional alveolar hypoxia, in which HPV might improve P_aO_2 by up to 20 mm Hg.[37]

Assessment of Gas Exchange

Besides clinical evaluation and noninvasive measures such as pulse oximetry, assessment of gas exchange rests on arterial

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blood gases. In addition to venous admixture and wasted ventilation, which require measurements that often are difficult to obtain, several other indices can be used to quantify and differentiate between causes of gas exchange impairment. Here we will mention some of them briefly, further reading is found in a prior review.[38]

Using P_aO_2 to evaluate gas exchange is more difficult when F_IO_2 is raised above 0.21. The $P_{A\text{-}a}O_2$ difference is increased by shunt, $\dot{V}_A/\dot{Q}$ mismatch, and diffusion limitation but not when hypoxemia is caused by low P_IO_2 (e.g., at high altitude) or by hypoventilation. The difference found in normal individuals increases with age and is very dependent on F_IO_2. The P_aO_2/F_IO_2 ratio is often used in clinical medicine because it is easily calculated, and it is included in the definition of the adult respiratory distress syndrome.[39] Even with unchanged $\dot{V}_A/\dot{Q}$ mismatch the ratio varies with changes in F_IO_2 and also with changes in arterial-venous O_2 extraction.[40–42] It is therefore not a perfect index for comparing the impairment of arterial oxygenation between two situations.

When P_aCO_2 is used to evaluate CO_2 elimination efficiency, it is necessary to take the minute ventilation into account. End-tidal PCO_2 ($P_{ET}CO_2$) is the PCO_2 of expired gas at the end of expiration, in practice the highest value recorded at the proximal airways during a respiratory cycle. $P_{ET}CO_2$ is used as a measure of mixed alveolar gas and as a surrogate measurement of P_aCO_2. With perfect $\dot{V}_A/\dot{Q}$ matching the P_aCO_2 to $P_{ET}CO_2$ difference is expected to be zero and in normal individuals the difference is low (<4 mm Hg) but increases with increased wasted ventilation. $P_aCO_2 - P_{ET}CO_2$ is however also dependent on several other parameters which might lead to both over- and underestimation of wasted ventilation.[38,43] Although $P_{ET}CO_2$ provides an estimate of PCO_2 in mixed alveolar gas, it does not correspond to the PCO_2 of mixed expired gas (P_ECO_2), which is used in the calculation of wasted ventilation. Due to the contribution of gas from the anatomical dead space ($PCO_2 \approx 0$), is much lower than $P_{ET}CO_2$. The ventilatory ratio (VR) is a relatively new measure that is calculated according to:

$$VR = \frac{\dot{V}_E \times P_aCO_2}{0.1 \times PBW \times 40}$$

where $0.1 \times PBW$ represents predicted $\dot{V}_E$ per kg predicted body weight and 40 is the normal P_aCO_2.[44] The ratio is therefore an aggregate estimate of CO_2 elimination efficiency that incorporates both minute ventilation and P_aCO_2. Remember that if $\dot{V}_A$ is halved, P_aCO_2 is expected to double. In theory this corresponds to an unchanged VR, i.e., it is consistent with unchanged CO_2 elimination efficiency, ignoring that doubled $\dot{V}_E$ might not equal doubled $\dot{V}_A$. VR is significantly influenced by $\dot{V}_{CO_2}$ and, similar to wasted ventilation, the effect of venous admixture on P_aCO_2, which hampers the use of VR to follow changes in dead space and high $\dot{V}_A/\dot{Q}$ regions.[45] VR has been reported for invasively ventilated patients with values from <1 to >5.[44,45]

Conclusion

Exchange of respiratory gases in the lung is facilitated by the large surface area over which blood and the alveolar space are in close proximity through the very thin membrane separating them. Variations in regional ventilation and perfusion that would make gas exchange less efficient are mitigated by the close matching of local perfusion and ventilation including by active matching of perfusion to ventilation through HPV. Venous admixture created by shunt and low $\dot{V}_A/\dot{Q}$ regions primarily causes hypoxemia while wasted ventilation due to dead space and high $\dot{V}_A/\dot{Q}$ regions results in inefficient ventilation and removal of CO_2. In comparison to an ideal situation with perfect match, $\dot{V}_A/\dot{Q}$ mismatch therefore leads to lower P_aO_2 and higher P_aCO_2 for a given minute ventilation, but the body responds by increasing minute ventilation to compensate for these cardinal signs of acute and chronic respiratory failure. Increased work of breathing is therefore a third, and sometimes the dominant, sign of acute and chronic respiratory failure.

Conflict of Interest
None declared.

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